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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/032,728	12/28/2001	Albert H. Olivencia-Yurvati	073314.0102	6388

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EXAMINER	
AFREMOVA, VERA	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 12/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/032,728	OLIVENCIA-YURVATI ET AL.	
	Examiner	Art Unit	
	Vera Afremova	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *1-6 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *7-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of claims

Claims 7-17 are under examination. Claims 1-6 and 18 are withdrawn.

Response to Arguments

Applicants' arguments filed 8/28/2003 have been fully considered but they are not all found persuasive for the reasons below.

Claim rejection under 35 U.S.C. 103(a) as being unpatentable over Hermann et al. [IDS-4 ref. QQ] has been withdrawn in the instant office action because the cited reference discloses a surgical protocol different from the claimed surgical protocol that requires a surgical access to a heart and an arrest of the heart.

However, it is noted that applicants appear to argue that the use of the Hermanns' reference solution containing pyruvate as a sole component would have been unacceptable when applied to the goal of the present invention (response page 5). Yet, the claimed invention indicates zero amounts of all components except pyruvate in the solution in the claimed method for performing surgery. Thus, the instant arguments in the light of the presently claimed invention are rather confusing.

Claim Objections

Claims 7-17 are objected to because of the following informalities:

Indication that NaCl, KCl, glucose, insulin, CaCl2 and lidocain are present at zero amounts in the solution in the method comprising heart arrest does not appear to be proper or have a reasonable meaning, particularly as related to the potassium concentration since

potassium is believed to be used for heart arrest. Applicants appear to acknowledge that solutions with pyruvate as a sole component would not arrest heart but increase cardiac performance.

Therefore, appropriate correction is required to avoid the claim language drawn to the sole use of pyruvate.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 7-17 remain rejected under 35 U.S.C. 103(a) as being unpatentable over WO 93/02653 [IDS-6 ref. H] taken with Rao et al. [IDS-6 ref. M], US 4,988,515 [IDS-4 ref. B] and Tejero-Taldo et al. [IDS-4 ref. RR] as explained in the prior office action and for the reasons below.

Claims are directed to a process for performing cardiopulmonary bypass surgery by administering a composition or a cardioplegia solution comprising pyruvate, NaCl, KCl, glucose, insulin, CaCl2 and lidocaine in amounts within the following ranges 0.2-50 mM pyruvate, 0-250 mM NaCl, 0-250 mM KCl, 0-200 mM glucose, 0-200 U/L insulin, 0-20 CaCl2 mM and 0-2 g/L lidocaine to the heart of a human patient in order to arrest the heart during the surgery. Some claims are further drawn to dilution of cardioplegia composition with whole blood prior administration at the ratio blood to solution such as 0.1-20 to 1. Some claims are further drawn to the intended effects of administration including protection of the heart from injury resulting from ischemia, rapid recovery of mechanical function, stabilization of heart energy reserves, antioxidant action and inotropic support.

The cited references are relied upon as explained in the prior office action and repeated herein.

WO 93/02653 teaches a process for performing cardiopulmonary bypass surgery comprising heart arrest during cardiac operations by administering directly to the heart of human patient a cardiopledgia composition or a cardioplegia emulsion/solution (example C, pages 19-20). The cardiopledgia emulsion of the cited WO document comprises components of crystalloid solutions including 100-150 mM NaCl, 5-20 mM KCl, 0.5-30 mM CaCl2, 5-300 mM glucose, pyruvate 5-100 mM and 0.1-0.5 mM lidocaine (table 1, page 11) wherein the concentrations of components are within the ranges as required by the presently claimed method. The emulsion in the clinical open-heart surgery as disclosed by the cited WO 93/02653 incorporates pyruvate as an optional ingredient and one of metabolic substrates (table 1).

The cited WO 93/02653 is lacking disclosure related to incorporation of insulin in the cardioplegia composition during cardiopulmonary bypass surgery including heart arrest.

However, the reference by Rao et al teaches a process for performing cardiopulmonary bypass surgery including heart arrest wherein in the method of Rao the cardioplegia solution comprises 10 IU/L insulin (abstract) as a beneficial component which provides for myocardial metabolic and functional recovery (abstract) of patients in need of cardiopulmonary bypass surgery.

Thus, both cited references WO 93/02653 and Rao et al disclose methods for performing cardiopulmonary bypass surgery including heart arrest by administering a composition/cardioplegia solution with the presently claimed ingredients within the presently claimed ranges. However, the cited WO 93/02653 and Rao et al are silent with regard to a

dilution of the cardioplegia solution with blood before administration of the cardioplegia solution.

However, US 4,988,515 teaches a process for performing cardiopulmonary bypass surgery wherein the cardioplegia solution is mixed with blood in the ratio blood to concentrated solution 4:1 (col. 4, lines 15-20). The cited patent also suggests to use the pyruvate containing cardioplegia solution (col. 4, line 5) for performing cardiopulmonary bypass surgery.

In addition, the cited reference by Tejero-Taldo et al. [IDS-4 ref. RR] is relied upon to demonstrate the beneficial effects of the pyruvate containing compositions in cardiac operations. For example: the reference teaches an antioxidant action of the pyruvate containing composition or cardioplegia solutions in the method comprising heart perfusion with cardioplegia solution (abstract) and it also discloses the role of pyruvate as natural fuel for the cardiac muscle, the role of pyruvate to potentate inotropic response and to prevent the energy depletion (introduction).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to combine chemical components of cardioplegia solution including pyruvate, NaCl, KCl, glucose, insulin, CaCl2 and lidocaine at concentration as taught and/or suggested by the cited references WO 93/02653 and Rao et al. in the method for performing cardiopulmonary bypass surgery in patients including human patients with a reasonable expectation of success because it is well known that it is prima facie obvious to combine ingredients which are taught by the prior art to be useful for the same purpose of performing cardiopulmonary bypass surgery in human patients in order to form a composition which is useful for the same purpose. The idea for combining the known components flows logically from their having been used separately in the prior art. In re Pinten, 459 F.2d 1053, 173

USPQ 801 (CCPA 1972); In re Susi, 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); In re Crockett, 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960). One of skill in the art would have been motivated to incorporate pyruvate in the cardioplegia solution in the method for performing cardiopulmonary bypass surgery in patients including human patients for the expected benefits in protecting the heart from injury resulting from ischemia, rapid recovery of mechanical function, stabilization of heart energy reserves, antioxidant action and inotropic support because these beneficial effects of pyruvate are well known in the prior art as adequately demonstrated by the disclosure of Tejero-Taldo et al. It is considered to be within the purview of one having ordinary skill in the art to adjust the final concentration of therapeutically effective amounts of cardioplegia solution by mixing blood with a concentrated cardioplegia solution in the method for performing cardiopulmonary bypass surgery in human patients as taught by US 4,988,515. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

With regard to the cited WO 93/02653 applicants argue that the solution in the particular example of a surgical protocol does not contain pyruvate (response page 6, last two par.). However, WO 93/02653 clearly suggests the use of pyruvate as an optional ingredient in the crystalloid solutions that are mixed with the fluorochemical emulsions in the surgical method including heart arrest during cardiac operations. Applicants' argument, that the recitation about dextrose as ingredient in the solution in the surgical method of example "C" (page 19) excludes

the use of pyruvate, does not have persuasive grounds because the cited WO 93/02653 clearly suggests incorporation of pyruvate in the crystalloid solutions that are mixed with fluorochemical emulsions (table 1) and the similar emulsion is administered in the surgical method of example "C" as disclosed by WO 93/02653 regardless the differences, if any, in the functional roles of dextrose or pyruvate. Moreover, both glucose and pyruvate are taught as metabolic substrates (table 1) and dextrose and glucose are different names of the same chemicals. Therefore, pyruvate and dextrose are equivalent metabolic substrates in solutions intended for cardiac operations in the light of teaching by WO 93/02653.

Applicants also appear to argue the significance of the differences between human and animal models (response page 7, par. 1). This instant argument is not considered to have persuasive grounds because WO 93/02653 teaches generic cardiac operations that encompass human surgery and the cited reference by Rao et al. clearly discloses a human surgery in particular examples. The specification paragraphs indicated by applicants have been reviewed. However, the argument drawn to the significance of the experimental data would not have any convincing grounds as argued for the claimed invention that does not indicate the proper amounts of materials used in order to evaluate the significance of the effects and/or results as intended.

With regard to the cited US 4,988,515 (Buckberg) applicants argue that it provides data for glucose/dextrose solution and, thus, the cited patent is deficient as related to the present invention. However, the cited patent is/was relied upon for the teaching of the limitation drawn to the blood: solution ratio (col. 4, line 20) in the composition introduced into the heart (col. 3, line 30) including human heart, for example: col. 9, line 21.

Claim rejection over Hermann' reference has been withdrawn as explained above because the cited reference does not disclose a surgery protocol requiring heart arrest.

With regard to the reference by Tejero-Taldo et al applicants argue that it does not provide a reasonably expectation in success because it is drawn to the animal or "guinea pigs" models rather than to the human models/applications. This is not found persuasive because pyruvate is universal metabolic substrate for all animals including humans and, thus, the beneficial effects of pyruvate applications are reasonably expected to be the same for all animal applications/models including human applications/models.

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351 till January 15, 2004 or (571) 271-0914 after January 15, 2004. The examiner can normally be reached on 9.30 am - 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (703) 308-4743 till January 15, 2004 or on (571) 272-0926 after January 15, 2004.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Vera Afremova

AU 1651

November 28, 2003.

V. Afremova

VERA AFREMOVA

PATENT EXAMINER